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ELECTIVE PARATHYROID SURGERY IN DIALYSIS PATIENTS WITH CHRONIC KIDNEY DISEASE (CKD) AND MORTALITY

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BACKGROUND

Hyperparathyroidism (HPT) is usually seen early in chronic kidney disease (CKD) and in most patients with CKD stage G5 or end stage renal disease (ESRD)[1]. CKD leads to hyperphosphataemia, low vitamin D levels and hypocalcaemia, resulting in diffuse parathyroid gland hyperplasia and subsequent rise in serum parathyroid hormone concentrations (PTH). Prolonged stimulation of the parathyroid glands leads to nodular hyperplasia and a reduction in calcium receptor density, resulting in resistance to most standard medical treatment[2,3]. Hyperparathyroidism manifests as one of two types of renal osteodystrophy and is associated with soft tissue and vascular calcification. This can lead to cardiovascular disease and contribute to the increased risk of morbidity and mortality among patients with CKD[4]. This area has recently been elucidated further with the identification of two important master switches in calcium phosphate regulation, FGF-23 and Klotho[5].

Conventional therapy includes dietary modification to reduce phosphate intake, the use of phosphate binders, calcium supplementation, vitamin D and its analogues and more recently the use of the calcimimetic agents (e.g. cinacalcet)[6]. Surgical management by parathyroidectomy (PTX) is considered in severe cases that are refractory to medical treatment and in those post transplantation where hyperparathyroidism persists despite reasonable renal function[7].

The literature suggests that the number of patients with HPT due to CKD who were managed by PTX decreased from 1990 to the late 1990's[8]. Further data from the United States however suggested that it had risen thereafter, despite an increase in the available medical management options in SHPT[9].

There is mounting data that disordered calcium phosphate metabolism is a risk factor for death in CKD patients[10], with the acceleration of cardiovascular disease in particular contributing to increased morbidity and mortality. It has been hypothesized that PTX modifies the mortality rate[11]. Studies of survival analyses suggest an increase in mortality rates post PTX, followed by a later recovery and improved survival when compared with medically matched patients[8, 12]. Another study suggested that survival was greater amongst patients who received an operation compared to those who did not; although there were potentially other confounding variables between the operated and non-operated groups[13].

This retrospective cohort review from a single, tertiary-care academic medical centre in the United Kingdom, primarily aims to determine the effect on mortality of parathyroidectomy for the management of HPT in patients with CRF and renal transplant recipients. Secondary outcomes of post-operative morbidity and success of procedure (restoration of normal calcium levels) are also considered.

METHODS

The study involved an observational cohort, taken from all dialysis and post-transplant patients with known CKD from Hull and East Yorkshire Hospital Services, United Kingdom, who underwent an elective parathyroidectomy over an 8-year period (2004 to 2012 inclusive). Participants were identified from prospectively collected patient data on the renal database at Hull Royal Infirmary.

All patients meeting the standardized criteria for surgical intervention of PTH level greater than 85 pmol/litre (800 pg/ml) refractory to standard therapy, and a normal or high adjusted serum calcium level were referred for surgery. All adult dialysis patients and post transplant patients who underwent a PTX were included in the study. Dialysis and post-transplant patients who did not undergo a PTX and were on the database from 2004 to 2012 were included for comparison. Patients who had dialysed for less than 90 days were not considered to be on chronic dialysis and were excluded from the analysis.

Data was collected on the following variables (Table 1):

- Age at the time of dialysis,
- Gender,
- Time spent on renal replacement therapy (RRT) divided into Haemodialysis (HD) and Peritoneal Dialysis (PD),
- Smoking status,
- The presence of co-morbid conditions at the initiation of dialysis, including: diabetes mellitus, ischaemic heart disease, angina,

cerebrovascular disease, peripheral vascular disease, chronic obstructive airway disease and non-dermatological malignancy.

- Survival (from time commenced on RRT to death or study end)

The NHS Hospital Trust Research and Development committee approved the study as part of regional development of its dialysis service. All patients are globally consented for use of patient data prior to initiating dialysis with the service as set out by the Trust's renal handbook policy. Formal written consent was not required as any subsequent interventions made during the observational study were aimed at improving clinical care based on the current guidelines, best available evidence and clinical expertise.

Operative Technique

All operations were performed by a single surgeon (JE), a four-gland PTX approach utilised. If a gland was not found then a search of recognised ectopic sites was undertaken. If a gland was still not evident inferiorly, a transcervical thymectomy was performed. If a gland was not evident superiorly, an ipsilateral level 6-7 fibrofatty clearance was performed. All glands were sent for histopathological assessment.

Statistical analysis

All continuous data were expressed as means and standard deviation (SD), medians and interquartile ranges for variables that are not normally distributed. All categorical variables were described in terms of percentage of total study population. These

variables were compared between groups using chi-square tests or Fishers Exact tests for categorical variables and t-tests for continuous data.

Mortality was the primary outcome measure at the time of censorship. Follow up started on the first episode of dialysis episode and continued until death or censoring as at 23/2/2012. Cumulative survival was calculated using the Kaplan–Meier method to compare PTX and non-PTX . The log-rank test was used to compare the survival curves and a Cox proportional hazards regression model was used to control for potentially confounding factors. Where there the factors indicated statistically significant differences between groups on univariate analyses ($p<0.1$), these were included in the regression model.

An additional analysis was undertaken to compare mortality among propensity-matched groups. Propensity matching was performed to minimize any selection bias due to the differences in the characteristics between PTX and non-PTX groups. For each patient in the cohort, a propensity score indicating the likelihood of being treated by PTX was calculated by the use of a non-parsimonious multivariable logistic regression model. Covariates included in the logistic regression model to calculate the propensity score were age, gender and year starting RRT. The Hosmer–Lemeshow test for goodness of fit was 0.701. To identify matched pairs of patients, a 1:1 optimal match with a ±0.03 calliper and no replacement was used. Cumulative survival was calculated using the Kaplan–Meier method.

Stata V.12 (StataCorp, College Station, Texas, USA) was used for statistical analysis. Probability values were two-sided, and values of $p<0.05$ were considered significant.

RESULTS

A total of 103 patients who had had a PTX and 1404 non-PTX were identified.

Table 1 shows the characteristics of the patients by group. The groups were similar in terms of sex, with 508/1404 (36%) female in the non-PTX group and 39/103 (38%) in the PTX group. The PTX patients were younger at their first RRT (46.3 (16.2)) than the non-PTX patients (57.7 (18.4), $p<0.001$). There was a statistically significant difference in malignancy rates ($p<0.001$), with higher malignancy in the PTX group (92% vs 83%). There was a statistically significant difference in diabetes ($p=0.004$), with higher rates in the PTX group (89% vs 72%). There was a statistically significant difference in HD days ($p<0.001$) and PD days (0.023). None of the other factors showed any statistically significant difference between groups.

There were 23/103 (22.3%) deaths in the PTX group and 695/1404 (49.5%) in the non-PTX group during the study period (to 23/2/2012). The mean time from first RRT to study end point or death was 76.5 months for the PTX patients compared to 49.6 months for non-PTX patients. In the PTX group the mean time from first RRT to operation was 62.2 (60.2) months.

Overall survival was higher in the PTX group as compared to the non-PTX group (Figure 1). The mean survival for the PTX group was 218.5 (21.7) months and 105.3 (4.3) months for the non PTX group. There was a statistically significant difference between groups (Hazard ratio 0.301; 95% CI: 0.199-0.457, p<0.001). After controlling for age (p<0.001) there was a statistically significant difference between groups (Hazard ratio 0.543; 95% CI: 0.356-0.827, p=0.004). As the PTX group had higher rates of malignancy and diabetes, a further model to control for these factors that indicated there was borderline statistical significance between groups (Hazard ratio 0.563; 95% CI: 0.309-1.029, p=0.062).

30 and 90 day survival for PTX patients

There were 5 deaths within 30 days (4.9%) and 6 within 90 days (5.8%) of operation. There was no statistically significant different in 30 day mortality between males and females (3.1% vs 7.7%, p=0.364) or 90 day mortality (4.7% vs 7.7%, p=0.671).

Propensity matching

Propensity matching resulted in 102 patients matched as one PTX patients couldn't be matched with a ±0.03 calliper. After propensity matching, no significant imbalance was identified in covariates between groups (Table 3). Overall survival was higher in the PTX group as compared to the non-PTX group (Figure 2). The mean survival for the PTX group was 218.0 (22.8) months and 87.1 (13.2) months for the non PTX group. There was a statistically significant difference between groups (Hazard ratio 0.248; 95% CI: 0.147-0.419, p<0.001). Hence similar results to those obtained using

the whole dataset. There were no significant differences between the PTX and non PTX groups for co-morbidities, so no further models were undertaken.

DISCUSSION

In this retrospective single centre observational study, we found that mortality was lower in patients who underwent elective PTX compared to those who did not undergo or require PTX based on criteria. Our finding in a UK population support recently published literature in other populations[12, 13,14, 15].

Comparisons with other studies

Kestenbaum et al[12] showed that patients undergoing PTX experienced an early increase in mortality risk within 30 days of surgery (3.1%) independent of gender or age, compared with matched medically managed patients. It was however associated with lower long-term risks of mortality in patients under 40 years of age when compared with matched patients not undergoing PTX. Their study had a larger sample size (n=4558); however a limitation of their study was that patient characteristics (including comorbidities and cardiovascular risk factors), unlike in ours, were not taken into account when calculating mortality rates. Other limitations included a lack of laboratory and medication data; and they therefore could not conclude which component might play in a role in their observed data.

Trombetti et al[13] performed a similar study, analysing survival after PTX in a cohort of patients in whom cardiovascular risk factors and comorbidities were considered. They found PTX patients were younger at first dialysis and had less comorbidity; and that their survival rate was higher compared to non-PTX patients. Only one PTX patient had died within one year of surgery, however their study had a small sample

size (n=40). Sharma et al[14] performed a retrospective and matched cohort study. In the first 30 days post surgery, 3 patients (n=150) had died (0.02%) which they stated represented a non-significant increased risk of death (p = 0.21). However they found that survival of patients treated with PTX was sustained for a decade when compared with medically managed patients. The mechanism for this wasn't clear; however a reduction in PTH, calcium and phosphate, and significant increases in albumin and haematocrit were noted. The majority of their patients maintained a postoperative serum PTH <600 pg/ml for up to 10 years. They also observed an overall reduction in mortality from cardiovascular diseases in their surgical cohort.

In the most recent study, Komaba et al[15] descibe their findings of a population-based cohort of Japanese patients on haemodialysis. As in our study, patients who underwent PTX had a reduced mortality (34% lower at 1 year post surgery) compared with matched non-surgical patients.

It is possible that patients undergoing surgery already have vascular compromise along with excess PTH, phosphate, activated vitamin D and calcium. These are factors that can increase the risk of death and therefore raise the postoperative mortality in the short term. PTX can also result in hungry bone syndrome. Essentially the ensuing postoperative hypocalcaemia requires prompt correction and lead to electrolyte shifts that can increase the risk of postoperative mortality[16].

Renal osteodytrophy is a major factor in the cardiovascular complications of CKD. One important factor is hyperphosphataemia leading to vascular calcification and cardiac disease. This is putatively due to increased FGF-23 levels leading to cardiac

changes such as left ventricular hypertrophy. Studies have suggested various mechanisms by which SHPT is linked with cardiovascular morbidity and mortality. Increased calcium cellular uptake and cardiac fibrosis have been shown experimentally secondary to raised serum PTH[17,18] and vascular calcification has been suggested as part of the pathophysiology[19,20]. Increased vascular calcification leads to abnormal cardiovascular physiology by way of arterial stiffening, left ventricular hypertrophy, plaque rupture and endothelial dysfunction[21].

Prolonged medical management of the hypercalcaemia associated with hyperparathyroidism may also contribute to diminished survival. One study has shown that higher doses of oral calcium binders were associated with coronary artery calcification[22]; and therefore reduced exposure to medical therapy in the long term post surgery may lower mortality. Further studies have shown that PTX can improve hypertension and anaemia[23,24], possibly contributing to lowering long term mortality rates.

Strengths of the study

The strengths of our study include surgery performed by a single surgeon and uniform management in a single centre. The limitations are the number of patients is relatively small and it is not a randomised control trial. It is an observational study and is prone to a degree of bias. Due to the lack of biochemical and medication and data, it isn't possible to state which exact component might be responsible for our observational findings.

CONCLUSION

In this observational study of UK patients with CKD, those who had PTX compared with the non-PTX group had an increased risk of postoperative mortality in the short term (up to 30 days from the day of surgery). However, in the long term, survival was higher in the PTX group. This difference was not attributed associated comorbidities after propensity matching was performed.

Conflicts of interest – none to declare

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Table 1: Descriptive characteristics of parathyroidectomy compared with the non-operative group

		Non-PTX n=1404		PTX n=103		Total		p-value
Age at the time of diagnosis		57.7 (18.4))		46.3 (16.2)		56.9 (18.5)		<0.001
Gender	Female	508	36%	39	38%	547	36%	0.736
	Male	895	64%	64	62%	959	64%	
Malignancy	No	958	83%	59	92%	1017	84%	0.059
	Yes	193	17%	5	8%	198	16%	
Angina	No	972	85%	53	83%	1025	85%	0.701
	Yes	177	15%	11	17%	188	15%	
MI<3m	No	1132	99%	63	98%	1195	99%	0.911
	Yes	16	1%	1	2%	17	1%	
MI>3m	No	1066	93%	61	95%	1127	93%	0.467
	Yes	81	7%	3	5%	84	7%	
CABG	No	1066	93%	58	91%	1124	93%	0.521
	Yes	83	7%	6	9%	89	7%	
Cerebrovascular disease	No	1038	90%	60	94%	1098	91%	0.365
	Yes	111	10%	4	6%	115	10%	
Diabetes	No	857	72%	57	89%	914	73%	0.003
	Yes	330	27%	7	11%	337	27%	
COPD	No	1070	93%	63	98%	1133	94%	0.106
	Yes	76	7%	1	2%	77	6%	
Liver Disease	No	1133	99%	64	100%	1197	99%	0.431
	Yes	11	1%	0	0%	11	1%	
Claudication	No	1057	92%	63	98%	1120	93%	0.063
	Yes	90	8%	1	2%	91	7%	
Ischaeminc europathic ulcers	No	1123	98%	64	100%	1187	98%	0.233
	Yes	25	2%	0	0%	25	2%	
Angioplasty	No	1085	95%	62	97%	1147	95%	0.414
	Yes	63	5%	2	3%	65	5%	
Amputation	No	1124	98%	63	98%	1187	98%	0.772
	Yes	24	2%	1	2%	25	2%	
Systemic Collagen Disease	No	575	97%	10	100%	585	97%	0.598
	Yes	16	3%	0	0%	16	3%	
Smoking	No	1010	89%	53	83%	1063	89%	0.118
	Yes	123	11%	11	17%	133	11%	
Heart Disease	No	269	88%	10	100%	279	89%	0.248
	Yes	36	12%	0	0%	36	11%	
PD days (Mean (sd))		275.6 (611.7)		420.4 (752.0)		285.5 (623.1)		0.023
HD days (Mean (sd))		827.6 (1032.2)		1853.9 (1595.8)		897.7 (1110.0)		<0.001

Table 2. A table to show the breakdown of the causes of chronic renal failure in both cohorts

	PTX patients n=103	%	Non-PTX patients n= 1404	%
Chronic renal failure – unknown aetiology	19	18.45	263	18.73
Diabetes (Type 1 and 2)	20	19.42	240	17.09
Glomerulonephritis	9	8.74	123	8.76
Chronic Pyelonephritis	15	14.56	120	8.55
Polycystic Kidney Disease	8	7.77	117	8.33
Renovascular Disease/hypertension	6	5.83	70	4.99
IgA Nephropathy	3	2.91	57	4.06
Wegener's Granulomatosis (GPA)	0	0	26	1.85
Obstructive Nephropathy	0	0	23	1.64
Reflux Nephropathy	3	2.91	9	0.64
Membranous Nephropathy	3	2.91	5	0.36
No documents available	1	0.97	38	2.71
Other	16	15.53	313	22.29

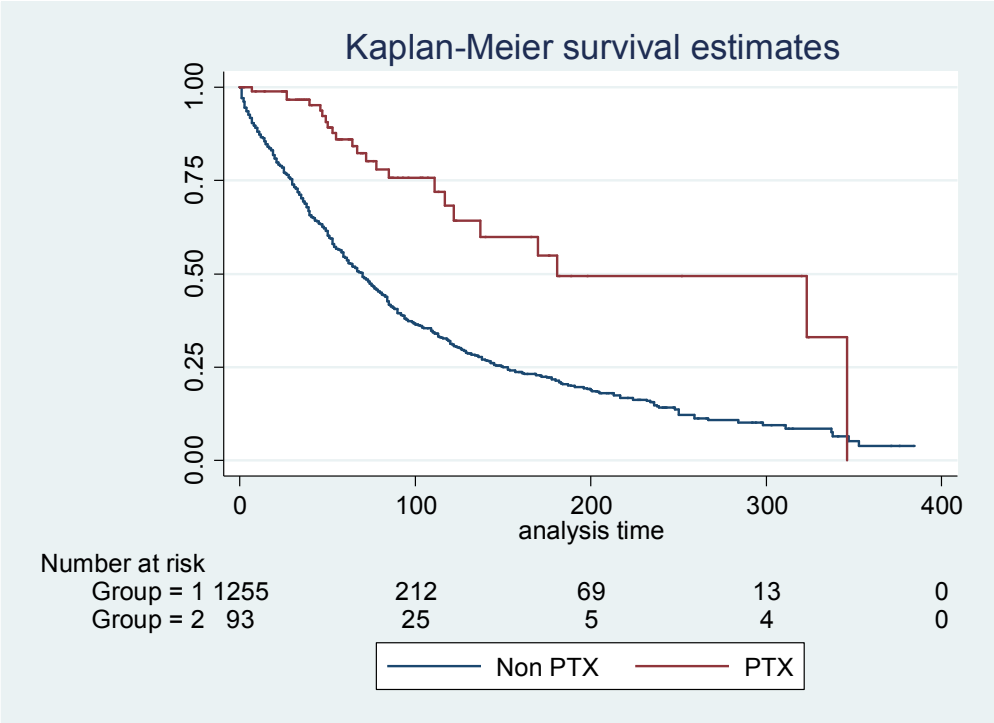
Table 3: Descriptive characteristics of propensity matched parathyroidectomy compared with the non-operative group

		Non-PTX n=102		PTX n=102		Total		p-value
Age at the time of diagnosis		45.9 (17.6)		46.5 (16.1)		46.2 (16.8)		0.797
Gender	Female	39	38.2%	39	38.2%	78	38.2%	0.999
	Male	63	61.8%	63	61.8%	126	61.8%	
Malignancy	No	79	90.8%	59	92.2%	138	91.4%	0.765
	Yes	8	9.2%	5	7.8%	13	8.6%	
Angina	No	78	89.7%	53	82.8%	131	86.8%	0.220
	Yes	9	10.3%	11	17.2%	20	13.2%	
MI<3m	No	87	100.0%	63	98.4%	150	99.3%	0.242
	Yes	0	0.0%	1	1.6%	1	.7%	
MI>3m	No	83	95.4%	61	95.3%	144	95.4%	0.979
	Yes	4	4.6%	3	4.7%	7	4.6%	
CABG	No	84	96.6%	58	90.6%	142	94.0%	0.128
	Yes	3	3.4%	6	9.4%	9	6.0%	
Cerebrovascular disease	No	84	96.6%	60	93.8%	144	95.4%	0.418
	Yes	3	3.4%	4	6.3%	7	4.6%	
Diabetes	No	74	82.2%	57	89.1%	131	85.1%	0.241
	Yes	16	17.8%	7	10.9%	23	14.9%	
COPD	No	82	94.3%	63	98.4%	145	96.0%	0.193
	Yes	5	5.7%	1	1.6%	6	4.0%	
Liver Disease	No	87	100.0%	64	100.0%	151	100.0%	-
	Yes	0	0.0%	0	0.0%	0	0.0%	
Claudication	No	83	95.4%	63	98.4%	146	96.7%	0.303
	Yes	4	4.6%	1	1.6%	5	3.3%	
Ischaeminc europathic ulcers	No	85	97.7%	64	100.0%	149	98.7%	0.222
	Yes	2	2.3%	0	0.0%	2	1.3%	
Angioplasty	No	81	93.1%	62	96.9%	143	94.7%	0.307
	Yes	6	6.9%	2	3.1%	8	5.3%	
Amputation	No	84	96.6%	63	98.4%	147	97.4%	0.476
	Yes	3	3.4%	1	1.6%	4	2.6%	
Systemic Collagen Disease	No	29	96.7%	10	100.0%	39	97.5%	0.559
	Yes	1	3.3%	0	0.0%	1	2.5%	
Smoking	No	78	89.7%	53	82.8%	131	86.8%	0.220
	Yes	9	10.3%	11	17.2%	20	13.2%	
Heart Disease	No	6	100.0%	10	100.0%	16	100.0%	
	Yes	0	0.0%	0	0.0%	0	0.0%	
PD days (Mean (sd))		284 (476.1)		374.7 (594.9)		329.7 (539.3)		0.234
HD days (Mean (sd))		849.4 (995.9)		1851 (1603.4)		1350.4 (1423.0)		<0.001

Legends for Figures

Figure 1: Kaplan –Meier estimates of cumulative survival among patients undergoing parathyroidectomy compared with the non-operative group

Figure 2: Kaplan –Meier estimates of cumulative survival among propensity matched patients undergoing parathyroidectomy compared with the non-operative group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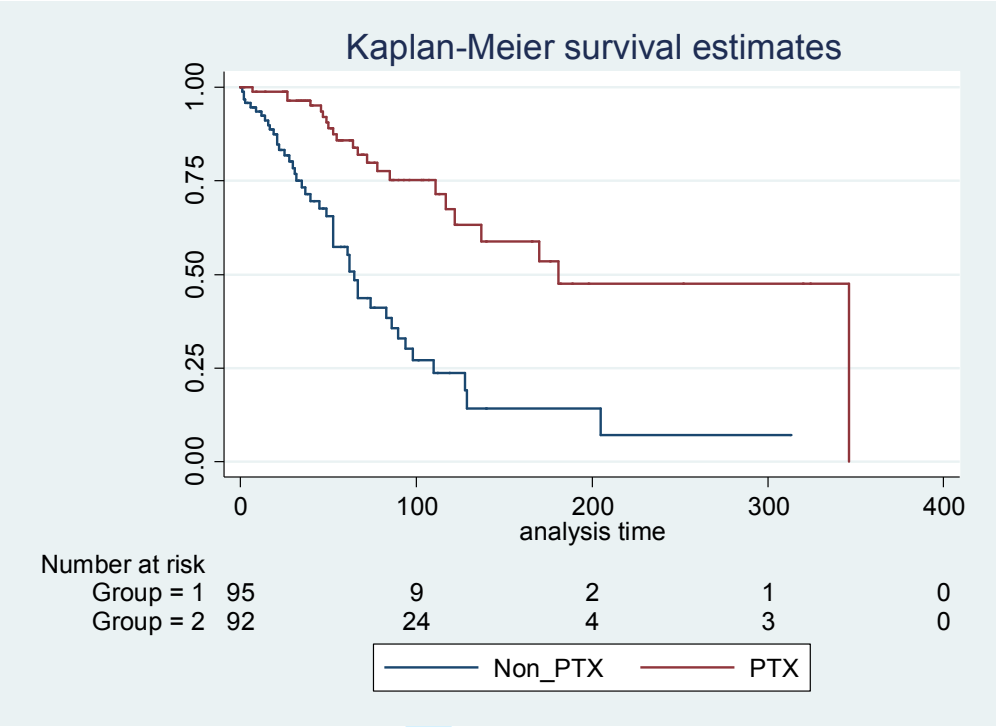
Kaplan-Meier survival estimates
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